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EDITORIAL COMMENT

The Stromal Cell–Derived Factor-1/CXCR4 Axis in Cardiac Injury and Repair*

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Chemokines are chemotactic cytokines that direct cellular migration through interactions with their cognate chemokine receptors. Most chemokines are not expressed in the normal myocardium, but are up-regulated and secreted in the infarcted heart (1), where they play an important role in leukocyte recruitment (2). Stromal cell–derived factor (SDF)-1/CXCL12 and its main receptor CXCR4 are a chemokine/chemokine receptor pair with unique functions in myocardial biology. Constitutive SDF-1/CXCR4 signaling in the myocardium is essential for cardiac development.

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Mice with targeted deletion of SDF-1 or CXCR4 exhibit embryonic lethality associated with impaired vascular formation and the development of ventricular aortopulmonary septum defects (3). In addition to its role in cardiovascular development, a growing body of evidence suggests that the SDF-1/CXCR4 axis is rapidly activated in the healing infarct (4), where it may exert protective actions by promoting angiogenesis, transducing prosurvival signals in cardiomyocytes, and enhancing the regenerative capacity of mobilized progenitor cells. Over the past 10 years, numerous studies have investigated the role of endogenous SDF-1/CXCR4 signaling in the repair of the infarcted heart and have explored the effects of SDF-1–based therapies in experimental myocardial infarction. The experiments have produced somewhat contradictory results, highlighting the complex, cell type–specific, and context-dependent actions of SDF-1/CXCR4 signaling in the infarcted heart.

In this issue of the *Journal*, Liehn et al. (5) studied the role of endogenous CXCR4 signaling in a model of nonreperfused myocardial infarction. Because CXCR4-null mice die perinatally, the authors used heterozygous $Cxcr4^{+/-}$ animals, which are phenotypically normal, but exhibit significantly lower cell surface Cxcr4 expression. When compared with wild-type animals, $Cxcr4^{+/-}$ mice had significantly reduced baseline coronary flow and exhibited impaired neoangiogenesis in the infarcted heart. Surprisingly, reduced coronary perfusion in $Cxcr4^{+/-}$ animals had no adverse functional consequences; $Cxcr4^{+/-}$ and wild-type animals had comparable post-infarction dysfunction and exhibited no difference in the density of apoptotic cardiomyocytes. The scars in $Cxcr4^{+/-}$ animals were smaller, probably reflecting accelerated wound contraction, and the leukocyte infiltrate in the infarcted heart contained fewer neutrophils and proinflammatory monocytes and an increased number of reparative Gr-1^{low} monocytic cells. The findings highlight the pleiotropic effects of CXCR4 signaling, suggesting that in the infarcted myocardium, the beneficial effects of CXCR4-dependent angiogenesis may be counterbalanced by its proinflammatory actions. Moreover, the study illustrates the limitations of genetically targeted mice in dissecting the pathophysiologic basis of disease. Attenuated CXCR4 signaling in heterozygotic animals was associated with a marked reduction in baseline cardiac perfusion that may have altered the susceptibility of cardiomyocytes to ischemic injury. These baseline alterations in cardiac physiology hamper understanding of the role of CXCR4 in ischemic injury, representing a significant challenge in interpretation of the findings. Despite these limitations, the study contributes new insights into the role of CXCR4 signaling in cardiac repair, providing evidence of both beneficial and detrimental effects of activation of the SDF-1/CXCR4 axis. Because CXCR4 signaling is a promising therapeutic target in myocardial infarction, several distinct experimental approaches have been used to explore its biological effects in the healing infarct.

Gain-of-function and pharmacologic inhibition experiments have served as the main tools with which to study the role of SDF-1/CXCR4 in cardiac repair; recently, conditional targeting approaches have also been used (Table 1) (6–17). In most studies, local infusion or overexpression of SDF-1 in the infarcted heart attenuated systolic dysfunction and reduced adverse remodeling. Three potential mechanisms of benefit have been suggested. First, SDF-1–mediated CXCR4 signaling may enhance infarct angiogenesis (6–9) through recruitment of endothelial progenitor cells (EPCs) or direct activation of angiogenic pathways. Second, SDF-1/CXCR4 signaling may protect ischemic cardiomyocytes from apoptosis through actions involving Erk and Akt activation (10). Third, SDF-1 may promote regeneration through recruitment of $Cxcr4^{+}$/c-kit^{+} progenitor cells (8). In contrast to the protective effects observed in most studies, an investigation using adenovirus-mediated gene therapy reported that CXCR4 overexpression in the infarcted heart accentuated inflammatory injury and in-

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Table 1 Experimental Studies Examining the Effects of SDF-1/CXCR4 Signaling in Myocardial Infarction

Strategy Used	Model	Main Findings	Ref. #
Gain-of-function studies			
Intramyocardial SDF-1 injection (300 ng) at the time of occlusion	Mouse (NR)	SDF-1 therapy improved systolic function, enhancing cardiomyocyte survival and increasing infarct angiogenesis.	(6)
Intramyocardial SDF-1 injection (1 μg) during occlusion	Mouse (NR)	SDF-1 therapy improved systolic function, reduced infarct size, and enhanced angiogenesis.	(9)
Intraventricular SDF-1 injection (35 μg/kg/min) for 5 min before occlusion	Mouse (R)	SDF-1 treatment reduced infarct size.	(10)
Intramyocardial injection of a protease-resistant SDF-1	Rat (NR)	SDF-1 therapy improved systolic function, inducing recruitment of $CXCR4^{+}$ progenitor cells and increasing angiogenesis.	(8)
Systemic infusion of SDF-1–overexpressing MSCs 1 day post-infarction	Rat (NR)	SDF-1–expressing MSCs increased angiogenesis and enhanced cardiomyocyte survival.	(7)
Systemic infusion of $CXCR4^{+}$ MSCs 3 days post-infarction	Rat (NR)	CXCR4-overexpressing MSCs had attenuated cardiac dysfunction associated with angiogenesis and myogenesis.	(16)
Transplantation of SDF-1–overexpressing fibroblasts 8 weeks after infarction	Rat (NR)	SDF-1–expressing fibroblasts induced homing of filgastrim-mobilized $CD117^{+}$ stem cells into the myocardium and improved cardiac function.	(4)
Adenovirus-mediated CXCR4 gene therapy 1 week before coronary occlusion	Rat (R)	CXCR4 overexpression accentuated myocardial inflammation, increased cardiomyocyte apoptosis, and worsened cardiac dysfunction.	(11)
Adenovirus-mediated SDF-1 overexpression 4 h post-infarction in animals receiving bone marrow-derived cells	Mouse (NR)	SDF-1 overexpression increased recruitment of bone marrow–derived cells in the infarct.	(17)
Pharmacologic inhibition studies			
Continuous subcutaneous infusion with the CXCR4 inhibitor AMD3100 for 20 days after occlusion	Mouse (NR)	Inhibition of the SDF-1/CXCR4 axis accentuated dysfunction and adverse remodeling.	(12)
Intraperitoneal and oral treatment with AMD3100	Rat (NR)	Inhibition of SDF-1/CXCR4 reduced infarct size and improved ventricular function.	(13)
a. Single-dose AMD3100 injection after the onset of infarction; b. continuous AMD3100 infusion	Mouse	Acute CXCR4 antagonism improved survival and reduced cardiac remodeling, increasing mobilization and recruitment of EPCs. In contrast, long-term CXCR4 inhibition accentuated adverse remodeling and impaired EPC incorporation in the infarct border zone.	(14)
Genetic loss-of-function studies			
Mice with congenital and conditional deletion of cardiomyocyte CXCR4 underwent infarction protocols	Mouse (NR)	Disrupted cardiomyocyte CXCR4 signaling did not affect cardiac repair and remodeling.	(15)
$CXCR4^{+/-}$ mice underwent infarction protocols	Mouse (NR)	Attenuated CXCR4 signaling was associated with reduced basal coronary flow. After infarction, $CXCR4^{+/-}$ mice had reduced angiogenesis and enhanced inflammatory activity. The severity of post-infarction systolic dysfunction was not affected by reduced CXCR4 signaling.	(5)

EPC = endothelial progenitor cell; MSC = mesenchymal stem cell; NR = nonreperfused infarction model; R = reperfused infarction model; SDF = stromal cell–derived factor.

creased activation of proapoptotic pathways, worsening cardiac dysfunction (11).

Pharmacologic inhibition of SDF-1/CXCR4 signaling using the selective small-molecule CXCR4 antagonist AMD3100 has also produced conflicting results. Long-term continuous inhibition of the SDF-1/CXCR4 axis in mice undergoing nonreperfused infarction protocols exacerbated systolic dysfunction and cardiac remodeling after infarction (12); these findings are consistent with the protective actions of CXCR4 signaling suggested by most gain-of function studies. However, other investigations demonstrated beneficial effects of CXCR4 antagonism. AMD3100 administration reduced infarct size and improved systolic function (13) in a rat model; however, the basis for these effects was not investigated. A recent investigation demonstrated that, although a single-dose AMD3100 injection administered after the onset of myocardial infarction preserved cardiac function, continuous infusion worsened the outcome (14). The beneficial effects of early CXCR4 antagonism were associated with increased mobilization of EPCs from the bone marrow. In contrast, the detrimental effects of long-term CXCR4 inhibition may be due to impaired incorporation of EPCs in the ischemic border zone (14).

The conflicting findings of studies interfering with the SDF-1/CXCR4 axis in the infarcted heart are due to the multifunctional and pleiotropic effects of CXCR4 signaling and to the complexity of the reparative process. CXCR4 signaling modulates phenotype and function of all cell types involved in cardiac repair; thus, in the dynamic environment of the healing infarct, functional outcome of strategies targeting the SDF-1/CXCR4 axis depends on timing and on the spatial localization of the intervention. Moreover, dose-dependent effects of SDF-1 on various cell types may affect the balance between angiogenic/reparative and proinflammatory actions of CXCR4 signaling. Dissection of cell- and time-specific effects of CXCR4 activation using conditionally targeted mice would be an important step for understanding the role of SDF-1 signaling in myocardial infarction. Using this type of approach, Agarwal et al. (15) demonstrated that CXCR4 signaling in cardiac myocytes does not play a crucial role in cardiac remodeling. Further work is needed to study the role of cell-specific and temporally restricted CXCR4-mediated ac-

tions in endothelial cells and leukocytes. Beyond their obvious mechanistic significance, such investigations would allow a more rational design of SDF-1–based strategies for patients with myocardial infarction.

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